Citation:

Crews WD Jr, Harrison DW, Wright JW. A double-blind, placebo-controlled, randomized trial of the effects of dark chocolate and cocoa on variables associated with neuropsychological functioning and cardiovascular health: clinical findings from a sample of healthy, cognitively intact older adults. *Am J Clin Nutr.* 2008 Apr;87(4):872-80.

PubMed ID: 18400709

Study Design:

Randomized Controlled Trial

Class:

A - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

NEUTRAL: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To examine the short-term (six weeks) effects of dark chocolate and cocoa on variables associated with neuropsychological functioning of healthy cognitively intact (CI) older adults as well as the cardiovascular health.

Inclusion Criteria:

- Healthy adults with 60 years old or higher
- No history of dementia or significant neurocognitive impairment
- Mini-Mental State Examination (MMSE) score of ≥24 out of 30

Exclusion Criteria:

- Active or clinically significant history of cardiovascular, neurological, pulmonary, endocrine, renal or urological, hepatic, gastrointestinal, or hematological disorders
- Uncontrolled hypertension or systolic BP higher than 160mm Hg and diastolic BP higher than 95mm Hg
- Total cholesterol higher than 300 mg/dL, HDL cholesterol lower than 30 mg/dL; total triacylglycerol higher than 400 mg/dL and CRP concentrations higher than 10 mg/dL
- Significant head injuries; episodes of anoxia or hypoxia, learning disabilities, color blindness, psychiatric or substance abuse disorders
- Use of medications such as: antihypertensive, hypolipidemic, nonsteroidal anti-inflamatory, anticoagulant or psychotropic

Description of Study Protocol:

Recruitment methods not reported

Design : Randomized controlled trial

Blinding used (if applicable): Double-blinded. The dark chocolate, cocoa beverage and placebo were matched for appearance, smell, taste, and caloric content.The products (chocolate, cocoa drink and placebo) were computerized randomized by an independent researcher. The boxes containing the products and their randomization numbers were issued to participants in an ascending and sequential order as they entered the study.

Intervention (if applicable):

- 37g dark chocolate bar and 8 oz (237 mL) of artificially sweetened cocoa beverage
- Similar placebo products
- Received each day for 6 week trial

Statistical Analysis:

- Two-factor mixed ANOVA and post hoc comparisons using Turkey's test
- Pearson chi-square analysis
- All values were expressed in mean and standard deviation

Data Collection Summary:

Timing of Measurements:

- Age, Education level, Mini-Mental State Examination score were assessed at baseline.
- Anthropometric and hematologic measurements, neuropsychological tests were assessed at baseline and end-of-treatment at six weeks.
- A self-reported medical and psychiatric histories questionnaire was also applied at baseline and at the follow-up after six weeks of treatment.
- However, blood pressure (BP), pulse rate and the Activation-Deactivation Adjective Check List, General Activation subscale (A-DACL) as one of the neuropsychological tests were taken at baseline, after three weeks of treatment and at the end (after six weeks).
- Treatment adherence was measured only at the end of the study (after six weeks) as well as the adverse effects.

Dependent Variables

- Neuropsychological tests**:** the Selective Reminding Test, the Wechsler Memory Scale-III Faces I and Faces II subtests, the Trail Making Test, the Stroop Color-Word Test, the Wechsler Adult Intelligence Scale-III Digit Symbol-Coding subtest, and the A-DACL
- Self-report medical and psychiatric histories questionnaire: the participants were initially screened by using this questionnaire developed by the two authors of this study
- Serum of total cholesterol, LDL-c, HDL-c, triacylglycerols, VLDL-c and CRP test
- BMI
- Blood pressure and pulse rate

Independent Variables

- Dark chocolate and cocoa drink vs placebo: the study used flavonoid-and procyanidin-rich dark chocolate bars and artificially sweetened cocoa beverage mix products, as well as low-polyphenol placebos. One dark chocolate bar (37g) contained 60% cacao, approximately 11g of natural cocoa, and 397.30 mg of proanthocyanins/g. One cocoa beverage (237mL or 8oz) had dry weight of 12g, with 11g of natural cocoa and 357.41 mg of total proanthocyanins/g. Placebo products were similar matched. Total proanthocyanin concentrations for each placebo bar and beverage were 0.20 mg/g and 40.87 mg/g, respectively.The products were taken orally on a daily basis and each participant were provided with a supply of randomly assigned boxes or containers with dark chocolate and cocoa or placebo products. Detailed instructions and forms onto which product consumption could be recorded daily were given with the products. Two hours before their scheduled assessments after three weeks at treatment and at the end of the treatment, participants were requested to consume either the dark chocolate bar or cocoa or the placebo matched products to ensure sustained doses. Treatment adherence was assessed via tabulations for the total amounts of dark chocolate and cocoa beverage or similar placebo products consumed; a deviation of 20% or more from the optimum treatment regimen was defined as nonadherence.

Control Variables

- Flavonoid and certain antioxidant intake: Participants using any chocolate- or cocoa-related products before entering the study were requested to terminate them seven days before the beginning of the study. They were also requested to avoid or, to the extent possible, limit their consumption of flavonoid-rich products such as blueberries, cranberries or cranberry juice, grapes or grape juice, red wine, soy, tea, pomegranate, acai, and isoflavone supplements for the duration of the study

Description of Actual Data Sample:

Initial N: 101 (41M;60F)

Attrition (final N): 90 (38M;52F)

Reasons for exclusion: From the dark chocolate/cocoa group; gastrointestinal upset or headaches (1), gastrointestinal upset and "cold sweats" (1), jitteriness and increased energy (1), atrial arrhythmia and medication changes (1), and distaste for the study products (1), bronchitis (1). Placebo group; gastrointestinal upset and constipation (1); distaste for the products (1), family illness (1); and unspecified personal reasons; nonadherence (1).

Age: mean age was 60 years or older

Ethnicity: not reported

Other relevant demographics: High level of education (15 years). All participants were healthy and cognitively intact adults. However, the total cholesterol and LDL-c were slightly to moderately above the reference ranges' cutoffs at baseline.

Anthropometrics: BMI was well matched with the placebo group at baseline. There was no difference between groups at the end of the study (25.09±3.47 vs 25.5±3.55 for chocolate bar group and placebo group, respectively).

Location: Lynchburg, VA

Summary of Results:

Key Findings

- No significant group-by-trial interactions were found for any of the neuropsychological variables examined
- There was no significant group-by-trial interactions for any of the hematologic tests or blood pressure variables
- The mean pulse rate after three and six weeks of treatment was significantly higher in the dark chocolate or cocoa group than at baseline ($P<0.01$) and when compared with the placebo group at the same period of time ($P<0.01$)

Hematologic test results

variables	Baseline		End-of-treatment		Change in score(baseline-end-of-treatment)		
	chocolate and cocoa group	Placebo group	chocolate and cocoa group	Placebo group	chocolate and cocoa group	Placebo group	P
Total cholesterol (mg/dL)	209.33±33.26	208.91±31.62	208.36±37.51	211.93±34.65	-0.98±19.24	3.02±16.26	0.290
LDL-c (mg/dL)	130.07±25.97	132.87±24.13	129.93±27.86	135.98±26.42	-0.13±16.82	3.11±14.7	0.333
VLDL (mg/dL)	15.27±7.92	15.84±6.95	15.44±7.63	17.56±8.22	0.18±5.06	1.71±5.45	0.170
HDL (mg/dL)	63.36±16.50	58.91±13.79	62.18±14.63	57.60±13.96	-1.18±5.79	-1.31±4.37	0.902
Triacylglycerol (mg/dL)	95.20±49.39	99.20±43.76	96.80±47.32	109.82±51.14	1.6±31.42	10.62±33.55	0.191
C-reactive protein (mg/L)	1.59±1.56	1.52±1.26	1.86±2.6	2.00±3.36	0.27±2.390	0.49±3.43	0.733

Other Findings

- There was a relationship between the treatment group to which participants had been assigned and the products that participants believed they had consumed; P=0.004. The follow-up questionnaire item on the treatment products that participants believed they had consumed during the trial showed that more than half (55.6%) of the participants from both groups correctly identified the products that they had ingested during the experiment
- The follow-up self-report questionnaire items concerning participants's subjective perceptions of changes from baseline to the end-of-treatment in their overall abilities and processes to remember, thinking, mood, energy levels, and health did not show any significant relation across five questions presented to the participants.

Author Conclusion:

The findings failed to support the predicted beneficial effects of short-term (six weeks) consumption of dark chocolate and cocoa on any of the neuropsychological or cardiovascular health-related variables included in this research. Consumption of dark chocolate and cocoa was, however, associated with significantly higher pulse rates at three and six weeks treatment assessments.

Reviewer Comments:

Small sample increases risk of type two error. Food intake was not assessed, therefore other sources of phytochemicals/isoflavones could be important confounders for the outcomes.

Additionally, the authors recognized the following limitations:

- *The relatively short duration of the treatment phase and the quantity of dark chocolate and cocoa products consumed may have contributed to the overall null findings;*
- *Whereas the possibility is speculative, a combination of greater product consumption and a relatively longer time span may have resulted more potent antioxidant and phytochemicals effects, which, in turn, could have been more readily measured or observed in such healthy, cognitively intact, older adults;*
- *Finally it seems that the groups were not fully blinded to the trial's products in light to the null findings from this study, however no evidence was found for any type of participant expectancy effects or bias that may have confounded the results*

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	Yes
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice?	Yes
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes

Validity Questions		
1.	**Was the research question clearly stated?**	Yes
1.1.	Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified?	Yes

1.2.	Was (were) the outcome(s) [dependent variable(s)] clearly indicated?	Yes
1.3.	Were the target population and setting specified?	Yes
2.	**Was the selection of study subjects/patients free from bias?**	No
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	No
2.2.	Were criteria applied equally to all study groups?	???
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	No
3.	**Were study groups comparable?**	???
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	???
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	No
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	N/A
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	N/A
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	**Was method of handling withdrawals described?**	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	No
4.4.	Were reasons for withdrawals similar across groups?	Yes
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A
5.	**Was blinding used to prevent introduction of bias?**	Yes
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	Yes
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	Yes
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A

5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were interveningfactors described?**	No
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	Yes
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	N/A
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	No
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	No
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	No
6.6.	Were extra or unplanned treatments described?	No
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	???
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	**Were outcomes clearly defined and the measurements valid and reliable?**	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	No
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	???
7.6.	Were other factors accounted for (measured) that could affect outcomes?	No
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**	No
8.1.	Were statistical analyses adequately described and the results reported appropriately?	No
8.2.	Were correct statistical tests used and assumptions of test not violated?	No
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	No
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes

	8.7.	If negative findings, was a power calculation reported to address type 2 error?	No
9.	**Are conclusions supported by results with biases and limitations taken into consideration?**		Yes
	9.1.	Is there a discussion of findings?	Yes
	9.2.	Are biases and study limitations identified and discussed?	Yes
10.	**Is bias due to study's funding or sponsorship unlikely?**		???
	10.1.	Were sources of funding and investigators' affiliations described?	Yes
	10.2.	Was the study free from apparent conflict of interest?	???